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PITUITARY ON FAT METABOLISM

A DISSERTATION SUBMITTED TO THE FACULTY
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THE ANTAGONISTIC EFFECT OF LIPOCAIC AND THE ANTERIOR PITUITARY ON FAT METABOLISM¹

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There is now general agreement that the activity of raw pancreas in preventing the deposition of fat in the livers of depancreatized dogs is not due to lecithin, choline, betaine, the enzymes of the pancreatic juice or to the general lipotropic action of protein. This activity is due to a specific substance, lipocaic, and the evidence indicating that this is a hormone distinct from insulin has been enumerated by Dragstedt (1). The suggestion by Best (2) that lipocaic is not a hormone but rather a specific dietary factor is probably a matter of definition.

The mode of action of lipocaic, except that in a general way it is concerned with the transport and utilization of fat, has remained relatively obscure. The characteristic changes in lipocaic deficiency: loss of body fat, accumulation of liver fat in large amounts, and hypolipemia are observed in depancreatized dogs in whom the other specific defects are corrected by the administration of pancreatic juice and insulin. These findings suggest a transport of depot fat to the liver and accumulation there due either to the increased rate of mobilization of fat or to an inability of the liver to further metabolize it. The administration of lipocaic corrects this metabolic abnormality in the depancreatized dog.

Abnormalities in fat metabolism similar to those seen in the insulin-treated depancreatized dog can be produced in smaller animals by the administration of certain anterior pituitary extracts. The first extract of this kind was prepared in 1930 by Burn and Ling (3). They termed the material ketogenic hormone because when they administered it to rats an increase in the urinary excretion of ketones was observed. The action of this substance was further studied by Anselmino and Hoffman (4) who found an accompanying increase in the blood ketones and in 1934 by Steppuhn (5) who showed that there was an increase in the fat content of the liver of rats receiving injections of the ketogenic hormone. Best and Campbell (6) studied the production of this type of fatty liver. In 1936 they confirmed the previous observations and noted that accompanying the increase in liver fat there was a decrease in the amount of body depot fat in fasted animals given the extract and that this decrease was greater than the decrease seen in the control fasted animals. The fat lost from the depots of the body was found to account for about one-half of the lipid recovered on analysis of the liver.

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² Submitted by Dr. Julian to the University of Chicago in partial fulfillment of the requirement for the degree of Ph.D. in surgery.

Best (7) had previously confirmed earlier work showing that large doses of choline would prevent the fatty liver of depancreatized dogs. Consequently, he tested the effect of choline on the fatty liver produced by anterior pituitary extracts and found no effect.

The purpose of the present study was to observe the effect of administration of lipocaic on the fatty liver produced by the injection of pituitary extracts. Further experimental work suggested by the results of this study is also reported.

This type of experiment had previously been made by McKay and Barnes in 1938 (8). These workers tested the effect of both choline and lipocaic on the ketogenic hormone fatty liver. The conclusion from their data was that neither substance had any effect. However, the pancreas extract was given in amounts which seemed to us to be too small to expect definite activity. They prepared lipocaic according to the method given in 1936 by Dragstedt, Prohaska and Harms (9); and, using rats, administered an amount of this extract equivalent to 8.7 grams fresh pancreas per square decimeter of body surface daily. This is approximately 30 grams fresh pancreas per day for a rat weighing 175 grams.

In the present study the lipocaic was purified for small animal work by the glacial acetic acid-ether method reported by Clark, Vermeulen, Donovan, and Dragstedt in 1939 (10). This method yields an average of 100 mgm. of extract from 200 grams of raw pancreas. In the work to be presented, daily doses of this extract ranging from 25 to 250 mgm., equivalent to 50 to 500 grams of raw pancreas, were given each animal. The preparation of the ketogenic hormone followed the method of Best and Campbell.

Three groups of young female guinea pigs weighing 300 to 375 grams were used. The initial weights were determined. All animals received only water by mouth during the 72-hour experimental period. Each animal in the three groups received an intraperitoneal injection after 24 hours and again after 48 hours of fasting. They were killed 24 hours after the second injection.

The animals in the control group received injections of 3 cc. of saline. The animals of the second group (group B) were given ketogenic hormone in doses varying from 2 to 10 mgm. per 100 grams of body weight. The animals of group C received similar amounts of ketogenic hormone plus total daily doses of 25 to 250 mgm. of lipocaic injected intraperitoneally at separate sites. At the completion of the 72-hour period the loss in the body weight, the final liver weight, and the percentage of lipid in the liver were determined. The total liver lipids and the milligrams of liver lipids per 100 grams final body weight were calculated. The results of these determinations are presented in table 1.

The average loss of body weight was greatest in both groups of animals receiving ketogenic hormone. This weight loss was not affected by the administration of lipocaic. The livers of the animals receiving ketogenic hormone were heavier than those that received additional lipocaic and than those of the control group.

The average percentage of liver lipids was found to be 11.1 in the control animals, 18 in the ketogenic hormone group, and 8.1 in the animals receiving lipocaic with the ketogenic hormone. The total liver lipids followed the same

pattern being 1138 mgm., 2677 mgm. and 1041 mgm. respectively in the three groups. To relate these figures to the sizes of the animals, the milligrams of liver lipid per 100 grams of final body weight are given. These calculated figures show very strikingly the protective action of lipocaic against the effect of ketogenic hormone.

This demonstration of an antagonistic relationship between lipocaic and the pituitary extract, ketogenic hormone, is important from the standpoint of the mechanism of lipocaic deficiency in the depancreatized dog. Does the insulin treated depancreatized dog develop a fatty liver as a result of the action of the anterior hypophysis, unopposed by lipocaic?

TABLE 1

Antagonistic effect of lipocaic on the fatty infiltration of the liver produced in guinea pigs by fasting and the injection of ketogenic hormone

NO. OF ANIMALS	AVERAGE INITIAL WT.	AVERAGE FINAL WT.	AVERAGE LOSS IN WT.	AVERAGE LIVER WT.	PER CENT LIVER LIPID			MGM. TOTAL LIPID IN LIVER			MGM. LIVER LIPID PER 100 GM. FINAL BODY WT.		
					High	Low	Aver.	High	Low	Aver.	High	Low	Aver.
Control group—3 cc. saline intraperitoneally													
6	gm. 349	gm. 298	gm. 51	gm. 9.9	16.5	5.2	11.1	1575	499	1138	496	172	375
Group B—1.5 to 10 mgm. ketogenic hormone per 100 gm. of animal intraperitoneally													
19	341	274	62	14.8	27.9	11.2	18	4525	1710	2677	1932	540	1011
Group C—1.5 to 10 mgm. ketogenic hormone per 100 gm. plus total dose of 25 to 250 mgm. of lipocaic preparation													
21	349	293	60	12.7	12.0	4.3	8.1	1480	425	1041	610	175	364

In order to examine further the rôle of the hypophysis in the fatty liver production in pancreatectomized dogs, a series of animals was first hypophysectomized and then depancreatized.

The results of this study are given in table 2. The dogs, nos. 1 to 6, survived the second operation from eleven to forty-two days. At autopsy the livers showed uniformly a marked increase in fat content, ranging from 22 to 42 per cent.

Dogs 7 to 10 were subjected to liver biopsy seven to forty-nine days after pancreatectomy. After biopsy the dogs were given lipocaic by mouth in doses known to cure fatty liver in pancreatectomized dogs. Following lipocaic administration for eight to one hundred and five days the dogs were sacrificed, usually at an attempted second biopsy, and a uniform decrease in liver fat observed. The liver of one of these dogs (no. 10) was biopsied after thirty-five days following pancreatectomy at which time the liver assay showed 43 per cent lipid. A second biopsy forty-one days later, lipocaic being given in the interval, showed 12 per cent fat in the liver. The dog died thirty-one days

after this second biopsy, and at this time a normal fat content of the liver was found.

The depancreatized, hypophysectomized dog develops a severe fatty liver in as short or shorter time than the dog with pancreatectomy alone. This fact has been infrequently observed in this preparation because most investigators using the Houssay animal have fed raw pancreas, containing lipocaic, as a food supplement.

This rapid appearance of the fatty liver in the Houssay animal indicates that the fat metabolism factor of ketogenic hormone is not the only factor in the

TABLE 2

Development of fatty infiltration of the liver in the hypophysectomized-depancreatized dog (Houssay) and response to lipocaic therapy

DOG	OPERATION DATES		DATE OF DEATH	LIVER FAT PER CENT WET WT.
	Hypophysectomy	Pancreatectomy		
				<i>per cent</i>
1	6/4	9/2	10/2	27
2	10/5	10/26	11/19	35
3	11/20	12/16	12/29	22
4	12/15	12/30	2/14	38
5	12/18	2/5	2/20	32
6	10/15	11/4	11/15	42

DOG	OPERATION DATES		LIVER BIOPSY		TREATMENT	LIVER POST-MORTEM	
	Hypophysectomy	Pancreatectomy	Date	Fat		Date	Fat
				<i>per cent</i>			<i>per cent</i>
7	11/26	12/3	1/3	32	Lipocaic 16 days	1/10	11
8	12/30	3/31	4/7	12	Lipocaic 8 days	4/15	9.9
						Perforated ulcer	
9	12/24	2/24	4/13	18	Lipocaic 3½ mo.	6/24	11
10	11/19	12/3	1/8	43	Lipocaic 2½ mo.	3/20	Normal liver
			2/19	12			

appearance of fatty liver in the depancreatized dog, though it may play a part in the lipid metabolism of the intact animal.

DISCUSSION. The antagonistic action of lipocaic and certain extracts of the anterior pituitary suggests that under normal conditions the transport of fat between the body depots and the liver is regulated by opposing hormone influences. It seems probable that the anterior pituitary liberates a substance into the circulation which causes a migration of body fat to the liver. Excessive breakdown of this fat results in hyperketonemia and ketonuria. Lipocaic, on the other hand opposes at least a part of this effect and causes the migration of fat to the body depots. Evidence with respect to the effect of lipocaic on the ketonemia and ketonuria resulting from injection of the ketogenic hormone is

not available. While the accumulation of fat in the liver of the depancreatized dog may be in part due to the unopposed action of the anterior pituitary in the absence of lipocaic, the fact that this accumulation occurs with equal rapidity in the "Houssay" animal indicates that this is not the sole mechanism.

CONCLUSIONS

1. The parenteral administration of lipocaic prevents the accumulation of fat in the liver produced by the injection of ketogenic hormone in fasting guinea pigs.
2. The fatty infiltration in the liver due to fasting is also decreased by the administration of lipocaic.
3. The Houssay animal develops the fatty liver of lipocaic deficiency just as rapidly as the depancreatized dog and is equally responsive to lipocaic therapy.
4. Some implications of the antagonistic action of lipocaic and the anterior pituitary on fat transport are mentioned.

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